(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 522 226 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **91830581.4**

(51) Int. Cl.5: **A61K 31/505**, A61K 9/08

(22) Date of filing: **20.12.91**

(30) Priority: **12.07.91 IT RM910519**

(43) Date of publication of application:
13.01.93 Bulletin 93/02

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR LI LU NL SE

(71) Applicant: **Costagliola, Ciro**
Via Francesco Petrarca 41/A
I-80122 Napoli(IT)

(72) Inventor: **Costagliola, Ciro**
Via Francesco Petrarca 41/A
I-80122 Napoli(IT)

(74) Representative: **Di Cerbo, Mario et al**
Società Italiana Brevetti S.p.A., Piazza di Pietra 39
I-00186 Roma(IT)

(54) Eyedrop solution for the treatment of ocular hypertension containing ketauserin.

(57) Eyedrop solution for the treatment of ocular hypertension characterized by the fact of consisting essentially of the combination of the following components expressed in percent by weight:

- from 0.01 to 2.0% of at least one hydrosoluble salt of ketanserin, for example ketanserin tartrate;
- optionally, from 0.01 to 10% of a substance that may stabilize the lacrimal film, selected preferably from the group comprising hydroxymethylcellulose, polyacrylic acid, propylenglycol, anhydrous dextrose and their combinations;
- optionally, from 0.001 to 0.01% of a preservative, for example benzalkonium chloride;
- optionally, a buffer system for maintaining the pH between the range 4.5 - 6.0, for example 0.1 - 1.0% of monopotassium phosphate and 0.1 - 1.5% of disodium phosphate;
- optionally, a colorimetric indicator that is biocompatible and pharmaceutically acceptable for revealing departures in the pH from the range 4.5 - 6.0;
- optionally, a solution that is isotonic with the osmotic pressure of the lacrimal fluid;
- optionally, at least one substance selected from the group comprising beta blockers, pilocarpine, alpha blockers, inhibitors of carbonic anhydrase, inhibitors of angiotensin converting enzyme and their combinations,

the balance up to 100% being water.

EP 0 522 226 A1

The present invention relates to an eyedrop solution for the treatment of ocular hypertension containing, at least as one of the active ingredients, a hydrosoluble salt of ketanserin, for example ketanserin tartrate.

It is known that the phenomenon of ocular hypertension can manifest itself at any age with an incidence of 0.5% of the total population of the Mediterranean races and of 1-2% of the total of the population of the Nordic races. This disease, if not treated in time and with the appropriate therapies inevitably leads to blindness. The state of progress of the research in the specific sector has led to the developments of topical therapies based on beta blocking adrenergic agents (beta blockers), pilocarpine and alpha blocking adrenergic agents (alpha blockers) or of systemic therapies with the use of carbonic anhydrase inhibitors.

The adoption of these drugs has moreover revealed to be not completely satisfactory. The use of beta blockers has counterindications in patients suffering from cardio-respiratory diseases (atrio-ventricular block, asthma and so on) and furthermore it induces lacrimal hyposecretion with consequent dry eye symptoms. The alpha blocking adrenergic agents and pilocarpine, on their part, acting on the pupillary sphincters, induce miosis with a consequent reduction of the visual capacity and the dark adaptation of the patient. Furthermore, pilocarpine is responsable for pathological alteration of the stroma of the iris and its prolonged use may produce cataracts. The inhibitors of carbonic anhydrase have counterindications in patients with prostatic hypertrophy, liver and kidney alterations, due to electrolyte imbalances provoked by them.

It has now been unexpectedly found that all these inconveniences may be overcome by adopting the eyedrop solution of the present invention. This eyedrop solution also offers other advantages that will be apparent hereinafter. The eyedrop solution of the present invention is characterized by the fact that it essentially consists of the combination of the following components expressed in percent by weight:

- from 0.01 to 2.0% of at least a hydrosoluble salt of ketanserin;
- optionally, from 0.01 to 10% of at least a substance that may stabilize the lacrimal film;
- optionally, from 0.001 to 0.01% of a biocompatible and pharmaceutically acceptable preservative ;
- optionally, a buffer system biocompatible and pharmaceutically acceptable for maintaining the pH in the range 4.5 - 6.0;
- optionally, a biocompatible and pharmaceutically acceptable colorimetric indicator, for revealing departures of the pH from the range 4.5 - 6.0;
- optionally, a solution that is isotonic with the osmotic pressure of the lacrimal fluid;
- optionally, at least one substance selected from the group comprising betablockers, pilocarpine, alpha blocking agents, inhibitors of carbonic anhydrase, inhibitors of the "angiotensin converting enzyme" (A.C.E.) and their combinations,

the balance up to 100% being water.

Good results have been obtained when at least one of the hydrosoluble salts of ketanserin was ketanserin tartrate.

The substance for the stabilizing of the lacrimal film may be selected from the group comprising hydroxymethylcellulose, polyacrylic acid, propylenglycol, anhydrous dextrose and their combinations.

The preservative can be, for example, benzalkonium chloride.

The buffer system, biocompatible and pharmaceutically acceptable, for maintaining the pH of the eyedrop solution in the range 4.5 - 6.0 may consist of 0.1 - 1.0% of monopotassium phosphate and 0.1 - 1.5% of monopotassium phosphate and 0.1 to 1.5% of disodium phosphate.

In the eyedrop solution, in a concentration of up to 1.0% in weight, the free acid corresponding to the hydrosoluble salt of ketanserin utilized may also be present.

The mechanism of action of the eyedrop solution according to the invention permits a more coherent therapeutic strategy than that for example of beta blockers (which represent the most effective treatment currently commercially available) with regard to the pathological manifestations of the glaucomatous disease. In fact, as known, in this disease the outflow of the aqueous humor is altered, and it has been seen that, while beta blockers act prevalently on the formation of the aqueous humor the eyedrop solution according to the present invention acts by improving the outflow of the aqueous humor compromised by the disease.

Up to now, a general description of the present invention has been given. With the help of the following example, representing a specific embodiment of the invention, further details will now be provided so as to better clarify its objects, characteristics, advantages and modality of application.

EXAMPLE

An eyedrop solution for the treatment of ocular hypertension according to the present invention has the following composition in percent by weight:

ketanserin tartrate	0.5%
propylenglycol	5.0%
anhydrous dextrose	5.0%
tartaric acid	0.1%,

the balance up to 100% of the composition being water.

The instillation of a drop (50 µl) of this eyedrop solution in the eye of a patient with chronic glaucome simplex produces a reduction in the ocular pressure from 25.3 to 20.7 mmHg after one hour. The obtained effect persists for approximately 12 hours. As a result a twice a day administration is sufficient.

The results obtained are comparable with those obtained using beta blockers that, amongst the active ingredients present in drugs currently available commercially, are the most effective for lowering the intraocular pressure. Moreover, the eyedrop solution according to the invention, contrarily to what happens for commercially available drugs containing beta blockers, can be administered to patients suffering from cardio-respiratory diseases and, in addition, does not induce a lacrimal hyposecretion with consequent dry eye symptoms in treated subjects.

Claims

1. Eyedrop solution for the treatment of ocular hypertension, characterized by the fact that it essentially consists of the combination of the following components expressed in percent by weight:
   - from 0.01 to 2.0% of at least a hydrosoluble salt of ketanserin;
   - optionally, from 0.01 to 10% of at least one substance for stabilizing the lacrimal film;
   - optionally, from 0.001 to 0.01% of a biocompatible and pharmaceutically acceptable preservative;
   - optionally, a biocompatible and pharmaceutically acceptable buffer system for maintaining the pH in the range 4.5 - 6.0;
   - optionally, a biocompatible and pharmaceutically acceptable colorimetric indicator for revealing departures of the pH from the range 4.5 - 6.0;
   - optionally, a solution that is isotonic with the osmotic pressure of the lacrimal fluid;
   - optionally, at least one substance selected from the group comprising beta blockers, pilocarpine, alpha blockers, inhibitors of carbonic anhydrase, inhibitors of the "angiotensin converting enzyme" and their combinations, the balance up to 100% being water.

2. Eyedrop solution for the treatment of ocular hypertension as per claim 1, in which the hydrosoluble salt of ketanserin is ketanserin tartrate.

3. Eyedrop solution for the treatment of ocular hypertension as per claims 1 or 2, in which the substance for the stabilization of the lacrimal film is selected from the group comprising hydroxymethyl cellulose, polyacrylic acid, propylenglycol, anhydrous dextrose and their combinations.

4. Eyedrop solution for the treatment of ocular hypertension as per any of the preceding claims, in which the preservative is benzalkonium chloride.

5. Eyedrop solution for the treatment of ocular hypertension as per any of the preceding claims, in which the biocompatible and pharmaceutically acceptable buffer system for maintaining the pH in the range 4.5 - 6.0 consists of 0.1 - 1.0% monopotassium phosphate and 0.1 - 1.5% disodium phosphate.

6. Eyedrop solution for the treatment of ocular hypertension as per any of the above claims from 1 to 5, which contains as a further component, at the expense of the water, up to 1% in weight of the free acid corresponding to the hydrosoluble salt of ketanserin used.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 83 0581

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	WO-A-9 102 527 (BETH ISRAEL HOSPITAL) * Claims 3,5,10-11,13-14; page 12, lines 24-34; page 13, lines 1-26 * ---	1-6	A 61 K 31/505 A 61 K 9/08
A	EP-A-0 268 309 (JANSSEN) * Claims; page 4, lines 5,20-33 * ---	1-6	
A	STN INTERNATIONAL INFORMATION SERVICES DATA BASE: CHEMICAL ABSTRACTS, vol. 106, no. 17, abstract no. 131570r, Columbus, Ohio, US, F.W. CHANG et al.: "Mechanism of the ocular hypotensive action of ketanserin", & J. OCUL. PHARMACOL., 1985, 1(2), 137-47 * Abstract * -----	1-6	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	09-09-1992	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)